Differences in the clinical profile and outcomes of typical and atypical takotsubo syndrome: data from the international takotsubo registry

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Abstract: IMPORTANCE: Apical ballooning is broadly recognized as the classic form of takotsubo syndrome (TTS). Atypical subtypes of TTS also exist, which constitute about 20% of all cases. To date, clinical profile and course of atypical TTS types have rarely been studied. OBJECTIVE: To characterize the clinical profile and outcomes of typical vs atypical types of TTS in a large patient cohort. DESIGN, SETTING, AND PARTICIPANTS: Records of 1750 patients from the International Takotsubo Registry, comprising 26 participating cardiovascular centers in 9 different countries, were reviewed and data on clinical profile and outcomes collected from January 1, 2011, to December 31, 2014. MAIN OUTCOMES AND MEASURES: Clinical characteristics and in-hospital as well as long-term outcomes were assessed. RESULTS: Of 1750 patients diagnosed with TTS between 1998 and 2014, a total of 1430 (81.7%) presented with apical TTS (defined as typical TTS) and 320 (18.3%) with midventricular, basal, or focal TTS (all defined as atypical TTS). Patients with atypical TTS were younger than those with typical TTS (mean [SD], 62.5 [13.3] vs 67.3 [12.9] years; P < .001). Brain natriuretic peptide levels on admission were lower (median factor increase of the upper limit of normal, 4.18 vs 6.59; P = .02) and left ventricular ejection fraction was higher (mean [SD], 43.4% [10.7%] vs 40.6% [12.0%]; P < .001) in patients with atypical than those with typical forms of TTS. ST-segment depression was more prevalent in patients with atypical TTS (31 of 286 [10.8%] vs 90 of 1292 [7.0%]; P = .03), while ST-segment elevation was found more frequently in patients with typical TTS (593 of 1292 [45.9%] vs 97 of 286 [33.9%]; P < .001). Patients with atypical TTS more often had neurologic disorders than those with typical TTS (81 of 274 [29.6%] vs 286 of 1251 [22.9%]; P = .02). While in-hospital mortality was comparable between patients with atypical and typical TTS (10 of 320 [3.1%] vs 62 of 1430 [4.3%]; P = .32), the atypical forms showed a favorable outcome at 1 year (P = .01). However, after adjustment for confounders, only left ventricular ejection fraction less than 45%, atrial fibrillation, and neurologic disease, but not the type of TTS, were independent predictors. After 1 year, patients with both types of TTS showed a similar prognosis at long-term follow-up. CONCLUSIONS AND RELEVANCE: Atypical TTS has different characteristics than typical TTS, including younger age of onset, more frequent ST-segment depression, higher prevalence of neurologic diseases, less pronounced reduction in left ventricular ejection fraction, and lower brain natriuretic peptide values on admission. Outcomes are comparable between patients with both types after adjustment for confounders, suggesting that both should be equally monitored.

DOI: https://doi.org/10.1001/jamacardio.2016.0225

Brief Report

Differences in the Clinical Profile and Outcomes of Typical and Atypical Takotsubo Syndrome
Data From the International Takotsubo Registry

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IMPORTANCE Apical ballooning is broadly recognized as the classic form of takotsubo syndrome (TTS). Atypical subtypes of TTS also exist, which constitute about 20% of all cases. To date, clinical profile and course of atypical TTS types have rarely been studied.

OBJECTIVE To characterize the clinical profile and outcomes of typical vs atypical types of TTS in a large patient cohort.

DESIGN, SETTING, AND PARTICIPANTS Records of 1750 patients from the International Takotsubo Registry, comprising 26 participating cardiovascular centers in 9 different countries, were reviewed and data on clinical profile and outcomes collected from January 1, 2011, to December 31, 2014.

MAIN OUTCOMES AND MEASURES Clinical characteristics and in-hospital as well as long-term outcomes were assessed.

RESULTS Of 1750 patients diagnosed with TTS between 1998 and 2014, a total of 1430 (81.7%) presented with apical TTS (defined as typical TTS) and 320 (18.3%) with midventricular, basal, or focal TTS (all defined as atypical TTS). Patients with atypical TTS were younger than those with typical TTS (mean [SD], 62.5 [13.3] vs 67.3 [12.9] years; $P < .001$). Brain natriuretic peptide levels on admission were lower (median factor increase of the upper limit of normal, 4.18 vs 6.59; $P = .02$) and left ventricular ejection fraction was higher (mean [SD], 43.4% [10.7%] vs 40.6% [12.0%]; $P < .001$) in patients with atypical than those with typical forms of TTS. ST-segment depression was more prevalent in patients with atypical TTS (31 of 286 [10.8%] vs 90 of 1292 [7.0%]; $P = .03$), while ST-segment elevation was found more frequently in patients with typical TTS (593 of 1292 [45.9%] vs 97 of 286 [33.9%]; $P < .001$). Patients with atypical TTS more often had neurologic disorders than those with typical TTS (81 of 274 [29.6%] vs 286 of 1251 [22.9%]; $P = .02$). While in-hospital mortality was comparable between patients with atypical and typical TTS (10 of 320 [3.1%] vs 62 of 1430 [4.3%]; $P = .32$), the atypical forms showed a favorable outcome at 1 year ($P = .01$). However, after adjustment for confounders, only left ventricular ejection fraction less than 45%, atrial fibrillation, and neurologic disease, but not the type of TTS, were independent predictors. After 1 year, patients with both types of TTS showed a similar prognosis at long-term follow-up.

CONCLUSIONS AND RELEVANCE Atypical TTS has different characteristics than typical TTS, including younger age of onset, more frequent ST-segment depression, higher prevalence of neurologic diseases, less pronounced reduction in left ventricular ejection fraction, and lower brain natriuretic peptide values on admission. Outcomes are comparable between patients with both types after adjustment for confounders, suggesting that both should be equally monitored.

JAMA Cardiol. 2016;1(3):335-340. doi:10.1001/jamacardio.2016.0225
Published online April 13, 2016.

Supplemental content at jamacardiology.com

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Takotsubo syndrome (TTS), also known as broken heart syndrome or stress cardiomyopathy, was first described in 1990[1] as transient apical ballooning of the left ventricle in the absence of obstructive coronary artery disease, predominantly present in female patients.[2] However, variants of this syndrome with midventricular,[3-6] basal,[7-11] and focal[12,13] wall motion patterns were later described. Interestingly, different forms of TTS can also occur in the same patient.[14]

As data on atypical forms of TTS are limited, knowledge of clinical features and outcomes is incomplete. This limited knowledge probably results in underdiagnosing of TTS, which poses a major risk to patients, as the adverse outcome of TTS still remains underrecognized.[15] The International Takotsubo Registry, which was founded to systematically investigate the disease, constitutes the largest cohort of TTS patients to date.[16]

The aim of our study was to provide a comprehensive characterization of features and outcomes of atypical TTS variants in the International Takotsubo Registry and to compare these forms to apical ballooning.

Key Points

Question What are the differences in clinical profile and outcomes between typical and atypical takotsubo syndrome (TTS)?

Findings Patients with typical and atypical TTS are characterized by distinct clinical profiles, and substantial but comparable in-hospital complication rates, including cardiogenic shock and death. One-year mortality is higher in patients with typical TTS, but after adjustment for confounders, only left ventricular ejection fraction less than 45%, atrial fibrillation, and neurologic disease, but not type of TTS, are independent predictors of death.

Meaning Patients with typical and atypical TTS should be equally and closely monitored.

Methods

Data Collection

The International Takotsubo Registry (http://www.takotsubo-registry.com) is an ongoing prospective and retrospective observational registry currently with 26 participating centers from 9 countries (eAppendix 1 in the Supplement). The first results on 1750 patients including general clinical features and outcomes have recently been published elsewhere.[16] A detailed description of the inclusion criteria, definition of the forms of TTS, and data collection is provided in eAppendix 2 in the Supplement.

Records of 1750 patients were reviewed and data on clinical profile and outcomes collected from January 1, 2011, to December 31, 2014. Follow-up included death from any cause and major adverse cardiac and cerebrovascular events (composite of recurrent TTS, myocardial infarction, stroke, or transient ischemic attack or death from any cause), which were assessed from medical records, telephone follow-up, or clinical visits. Complete details on follow-up have been recently reported.[16] The study protocol was reviewed by the respective local ethics committees or investigational review boards at each collaboration site. Due to the in part retrospective nature of the study, ethics committees of most study centers waived the need for informed consent. At centers in which the ethics committees or investigational review boards required informed consent or in which patients were included prospectively, formal written consent was obtained from patients or surrogates.

Statistical Analysis

Differences between groups were calculated using the Pearson χ^2 test or the Fisher exact test. Laboratory parameters were compared using the Mann-Whitney test and Kruskal-Wallis test. The remaining continuous data were compared using an unpaired *t* test and one-way analysis of variance. Survival was analyzed using Kaplan-Meier estimates and log-rank test, as well as a landmark analysis with a landmark set at 1 year. Statistical analyses were performed using SPSS, version 22.0 (IBM Corp). $P < .05$ (2-sided) was considered statistically significant. All graphs were compiled with Prism 6 (GraphPad).

Results

Patient Characteristics

Atypical TTS was present in 320 patients (18.3%), including the midventricular (255 [14.6%]), basal (39 [2.2%]), and focal (26 [1.5%]) forms (**Figure 1**; eTable 1 in the Supplement).[16] During the period from 1998 to 2014, atypical TTS was increasingly diagnosed (eFigure 1 in the Supplement). Patients with atypical TTS were younger than patients with typical TTS ([SD], 62.5 [13.3] vs 67.3 [12.9] years; $P < .001$), and patients with basal TTS were the youngest among the subgroup of those with atypical TTS (**Table**; eTable 1 and eTable 2 in the Supplement). There were no differences between patients with typical and atypical TTS in symptoms on admission and emotional ($P = .09$) or physical ($P = .46$) triggering factors; however, a subgroup analysis revealed that the basal form most often occurred without an identifiable trigger (17 of 39 [43.6%] [Table; eTable 1 and eTable 2 in the Supplement]).

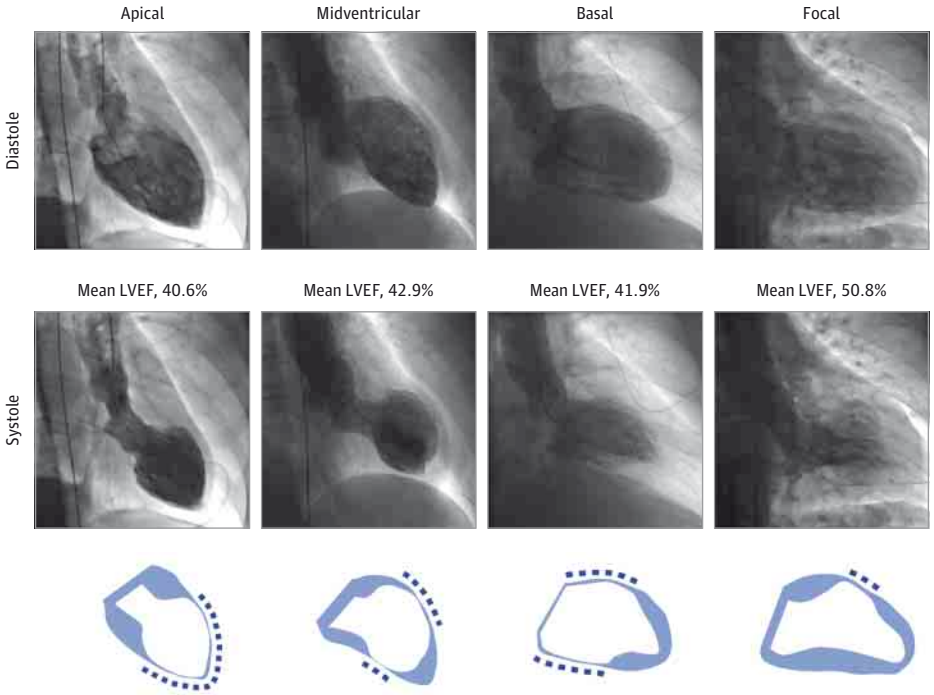
Laboratory Values

On admission, levels of brain natriuretic peptide (BNP) were higher in patients with typical TTS than those with atypical TTS (median factor increase of the upper limit of normal, 6.59 vs 4.18; $P = .02$). In contrast, levels of troponin and creatine kinase were not different between both groups. Levels of C-reactive protein on admission were higher in patients with typical vs atypical TTS (eTable 2 in the Supplement).

Electrocardiogram Results

Compared with those with atypical TTS, patients with typical TTS more often had atrial fibrillation (7.7% [100 of 1298] vs 4.2% [12 of 286]; $P = .04$), ST-segment elevation (45.9% [593 of 1292] vs 33.9% [97 of 286]; $P < .001$), and T-wave inversion (42.4% [548 of 1292] vs 35.0% [100 of 286]; $P = .02$). In contrast, ST-segment depression was more

Figure 1. Four Different Wall Motion Patterns in Takotsubo Syndrome



Left ventricular angiograms in right anterior oblique view (30°) during diastole and systole demonstrating the 4 different subtypes of takotsubo syndrome: apical, midventricular, basal, and focal. The lower row shows the schematic of wall motion abnormalities corresponding to the angiograms above (blue, diastole; white, systole; blue dashed line, affected regions). LVEF indicates left ventricular ejection fraction.

prevalent among patients with atypical TTS (10.8% [31 of 286] vs 7.0% [90 of 1292]; $P = .03$), particularly in those with the basal form (7 of 38 [18.4%]). While duration of QTc as a hallmark of TTS did not differ between patients with typical and atypical TTS (mean QTc, 458.7 vs 452.7 milliseconds; $P = .08$), those with the basal form exhibited significantly longer QTc times (mean, 477.3 milliseconds; $P = .01$) (Table; eTable 1 and eTable 2 in the Supplement).

Hemodynamic Findings

Patients with typical TTS had a lower left ventricular ejection fraction (LVEF) on admission (mean [SD], 40.6% [12.0%] vs 43.4% [10.7%]; $P < .001$) than patients with atypical TTS, with the focal form having the highest LVEF (mean [SD], 50.8% [13.6%]) (Figure 1, Table; eTable 1 and eTable 2 in the Supplement). Of note, LVEF recovered to normal levels irrespective of the initial form of TTS (eFigure 2 in the Supplement).

Neurologic and Psychiatric Comorbidities

Patients with typical TTS more often presented with an acute psychiatric episode than those with atypical TTS (10.5% [132 of 1254] vs 6.3% [17 of 271]; $P = .03$), while patients with an atypical form more often presented with a neurologic disorder (29.6% [81 of 274] vs 22.9% [286 of 1251]; $P = .02$) (Table; eTable 2 in the Supplement).

Outcomes

There were no significant differences between patients with typical and atypical TTS regarding the incidence of in-hospital complications, such as cardiogenic shock (10.5% [147 of 1404] vs 7.4% [23 of 312]; $P = .10$), and in-hospital death (4.3% [62 of 1430] vs 3.1% [10 of 320]; $P = .32$) (Table; eTable 2 in the Supplement). The focal form of TTS showed the most favorable outcome, with no cases of cardiogenic shock or in-hospital death (eTable 1 in the Supplement). Accordingly, the frequency of acute cardiac care did not differ between patients with typical and atypical TTS (20.1% [285 of 1421] vs 23.9% [75 of 341]; $P = .13$) (eTable 2 in the Supplement).

Long-term follow-up demonstrated comparable rates of major adverse cardiac and cerebrovascular events in patients with typical and atypical TTS (10.0% vs 9.2%, respectively; $P = .42$), while the difference in mortality showed borderline significance between the groups (6.0% vs 3.9%, respectively; $P = .05$; eTable 2 in the Supplement). We therefore performed a landmark survival analysis, showing a substantially increased mortality rate at the prespecified landmark of 1 year in patients with typical TTS ($P = .01$); however, after that point, mortality rates were comparable between both types of TTS ($P = .99$; **Figure 2**). More important, results of a multivariate analysis revealed that the type of TTS was not an independent predictor of mortality at 1 year, in contrast to LVEF less than 45%, atrial fibrillation, and the presence of neurologic disease (eFigure 3 in the Supplement).

Discussion

This study is the first, to our knowledge, to determine clinical characteristics and outcomes of patients with atypical TTS in a large patient population. We found several differences

Table. Characteristics of Patients with TTS

Characteristic	Value[a] Typical TTS (n = 1430)	Atypical TTS (n = 320)	*P* Value
Demographics			
Female sex	1284 (89.8)	287 (89.7)	.96
Age, mean (SD), y	67.3 (12.9)	62.5 (13.3)	<.001
Triggers			
Physical	509 (35.6)	121 (37.8)	.46
Emotional	384 (26.9)	101 (31.6)	.09
Both emotional and physical	111 (7.8)	26 (8.1)	.83
No evident	426 (29.8)	72 (22.5)	.009
Symptoms on admission			
Chest pain	1014 of 1325 (76.5)	215 of 294 (73.1)	.22
Dyspnea	623 of 1320 (47.2)	137 of 300 (45.7)	.63
ECG on admission			
ST-segment			
Elevation	593 of 1292 (45.9)	97 of 286 (33.9)	<.001
Depression	90 of 1292 (7.0)	31 of 286 (10.8)	.03
Hemodynamic findings, mean (SD)			
Heart rate, beats/min	87.9 (21.5)	85.8 (23.3)	.15
No. of patients	1173	274	
Systolic blood pressure, mm Hg	130.3 (29.1)	132.1 (27.6)	.33
No. of patients	1168	280	
Left ventricular ejection fraction, %[b]	40.6 (12.0)	43.4 (10.7)	<.001
No. of patients	1312	287	
Neurologic or psychiatric disorders[c]	580 of 1251 (46.4)	134 of 274 (48.9)	.45
Neurologic disorders, total[c]	286 of 1251 (22.9)	81 of 274 (29.6)	.02
Acute	110 of 1255 (8.8)	33 of 273 (12.1)	.09
Past or chronic	229 of 1238 (18.5)	64 of 274 (23.4)	.07
Psychiatric disorders, total[c]	404 of 1251 (32.3)	88 of 274 (32.1)	.96
Acute	132 of 1254 (10.5)	17 of 271 (6.3)	.03
Past or chronic	360 of 1238 (29.1)	84 of 274 (30.7)	.60
In-hospital complications and management			
Cardiogenic shock	147 of 1404 (10.5)	23 of 312 (7.4)	.10
Death	62 (4.3)	10 (3.1)	.32
Cardiopulmonary resuscitation	128 of 1421 (9.0)	21 of 314 (6.7)	.18
Invasive or noninvasive ventilation	241 of 1421 (17.0)	60 of 314 (19.1)	.36
Catecholamine use	177 of 1421 (12.5)	35 of 314 (11.1)	.52

Abbreviations: ECG, electrocardiogram; TTS, takotsubo syndrome.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Data obtained during catheterization or echocardiography; if both results were available, data from catheterization were used.

[c] Category includes patients with either an acute as well as past or chronic disorder.

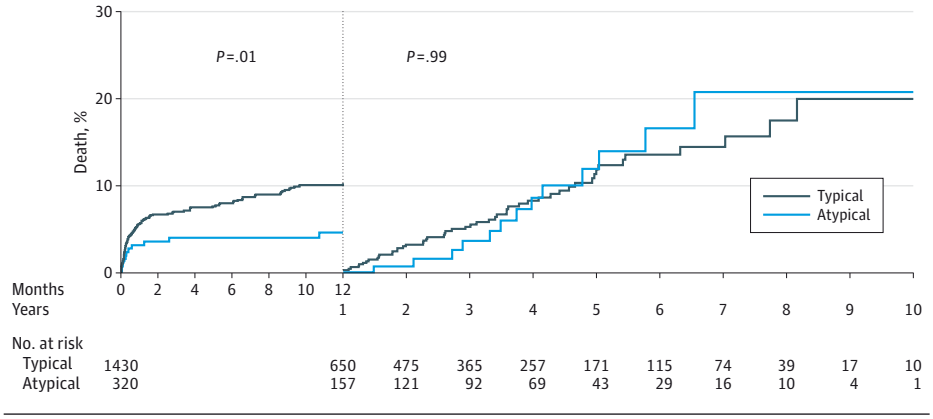
between patients with atypical and typical TTS. Patients with atypical TTS are slightly younger than those with typical TTS and more often experience neurologic comorbidities. Therefore, one may speculate that neurologic disorders alter a patient's susceptibility for TTS in general as well as particular patterns of wall motion abnormalities in response to a triggering event.

Typical TTS usually affects a large extent of the myocardium. The BNP levels were consistently higher and LVEF was lower in patients with typical TTS compared with those with atypical TTS. The most preserved LVEF was found in patients with focal TTS. Thus, TTS occurs in a spectrum of different phenotypes, with focal TTS appearing as the mildest variant of the disease.

Contrary to the common belief that triggering factors might differ between types,[11,17] our data show that the prevalence of emotional or physical triggers is comparable between groups. This finding demonstrates that the small sample sizes in previous studies can exert a profound limitation. We further speculate that individuals who present with a triggering factor have a higher probability to be diagnosed with TTS than those without such factors, representing a relevant awareness bias during clinical routine.

It appears likely that the different wall motion patterns in patients with typical and atypical TTS translate into differences in ECG patterns. Although previous studies did not find such differences,[18] we identified significantly more frequent ST-segment elevations and T-wave inversions and less frequent ST-segment depressions in patients with typical TTS. Considering the higher BNP values, lower LVEF, and larger affected area of the myocardium in the presence of rather low creatine kinase and troponin levels compared with acute

Figure 2. Mortality in Typical and Atypical Takotsubo Syndrome



Landmark survival analysis demonstrates a significantly higher mortality rate in patients with typical takotsubo syndrome during the first year (P = .01). Thereafter, mortality was comparable between patients with typical and atypical types (P = .99). Kaplan-Meier estimates, log-rank test.

coronary syndrome (ACS), it is tempting to speculate that changes on ECG results seen in TTS reflect myocardial stunning and reversible damage rather than ischemia or necrosis.

Takotsubo syndrome is usually recognized as a transient benign disease; however, Templin et al[16] demonstrated that in-hospital complications are comparable between patients with TTS and those with ACS. Regarding the differences in wall motion patterns and left ventricular function, we hypothesized that the outcome of typical TTS is worse than that of atypical TTS. However, despite the younger age, higher LVEF, and lower BNP values in patients with atypical TTS, the rate of severe in-hospital complications (eg, lethal arrhythmias, cardiogenic shock, or death) was as high as in patients with typical TTS. Thus, all types of TTS should be monitored as closely as patients with ACS.

Long-term follow-up demonstrated that the borderline significance in mortality was in fact driven by the difference in the first year after the event. However, adjustment for potential confounders revealed that the type of TTS was not an independent predictor of mortality. We can only speculate that patients with typical TTS have a longer time to recovery and increased incidence of atrial fibrillation, thereby explaining that LVEF is an independent predictor of mortality. Moreover, our data also propose that other factors beyond the type of TTS (such as neurologic disease) may contribute to increased mortality in patients with typical TTS.

Retrospective observations have inherent limitations but are of critical value for elucidating understudied diseases. Notwithstanding the grown expertise in TTS diagnosis in all participating centers, a referral bias cannot be excluded.

Conclusions

Our study emphasizes that atypical TTS accounts for nearly 20% of all cases of TTS and has different clinical features than typical TTS, including younger patient age, more frequent ST-segment depression, higher prevalence of neurologic disease, less impaired LVEF, and lower BNP values. Of all forms, focal TTS appears to have the most favorable outcome. Comparison of patients with typical and atypical TTS reveals similar in-hospital complication rates and outcomes. LVEF less than 45%, atrial fibrillation, and the presence of neurologic disease are independent predictors of death at 1-year follow-up.

ARTICLE INFORMATION

Accepted for Publication: February 8, 2016.

Published Online: April 13, 2016. doi:10.1001/jamacardio.2016.0225.

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Acquisition, analysis, or interpretation of data: All authors.
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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Napp reported receiving nonfinancial support outside this study from Medtronic, Biotronik, Abbott, Lilly, Servier, Volcano, Boston Scientific, Pfizer, and Bayer. Dr Templin reported receiving support outside this study from Abbott Vascular, Boston Scientific, Edwards Lifesciences, Medtronic, and Biosensors. No other disclosures were reported.

Funding/Support: This study was funded by grants from the Mach-Gaensslen Foundation, Olten Heart Foundation, Prof Otto-Beisheim-Foundation, and Swiss Heart Foundation (Dr Templin), and a research grant from the Olten Heart Foundation and a research grant "Filling the gap" from the University of Zurich (Dr Ghadri).

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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